Sulfonamyl Diuretics

Mechanism of Action and Therapeutic Use

KATHLEEN E. ROBERTS, *M.D.*, Toledo, Ohio

• **The mechanism whereby sulfonamyl diuretics are effective is through the blockage of the renal tubular reabsorption of chloride. The excretion of sodium, potassium and water is a passive one to maintain ionic equilibrium. Chlorothiazide has been shown to be almost ineffective as a diuretic agent *per se*. Although it does block a moiety of the renal tubular reabsorption of bicarbonate, the effect is merely a transient one.**

IN THE TIME since it was first noted that certain cyclic sulfonamide diuretics may cause diuresis, many analogues of these agents have been developed for clinical use. Although less effective than the organic mercurial diuretics, they warrant attention because of their increasing clinical popularity and the ease of administration. They have the advantage of being useful when given either orally or intravenously. Most of them have little toxicity and they are therapeutically effective not only in edema due to various causes, but also in obesity and as weakly hypotensive agents.[1-7,12]

Among the various sulfonamyl diuretics which have evolved for clinical use, there are two general classifications, which accord with their physiological effects—the acetazolamide group and the thiazide group. Although these two groups are generally characterized as having similar effects on the renal excretion of water and electrolytes in dogs, this is not the case in humans.[8] Hence, the separate categories.

ACETAZOLAMIDE

Acetazolamide (Diamox®) when given intravenously in doses of 2 to 3 gm will alkalinize the urine acutely both in human subjects and animals. When given in smaller doses, it has little if any diuretic or alkalinizing effect.

When given in such large amounts intravenously, its immediate action is to block the renal tubular reabsorption of bicarbonate, as illustrated in Figure 1. Its mechanism of action is to increase the intracellular pH and cause temporary, short-lived diuresis. The reabsorption of bicarbonate is dependent in large part on the intracellular pH of the renal tubules. When this is alkaline, bicarbonate reabsorption is decreased.[8,10,11]

As is illustrated in Figure 1, the blockage of carbonic anhydrase inhibits the formation of carbonic acid. In the intracellular fluid, as in the extracellular fluid, the ratio of bicarbonate to carbonic acid determines, in part, the cellular pH. In renal tubular cells, the bicarbonate is bound as potassium bicarbonate. If the carbonic acid decreases and potassium is unchanged, the cellular pH will become more alkaline. However, the renal tubular alkalinization and diuresis is transient, since the renal tubules quickly accommodate to the inhibition of carbonic anhydrase, and by "mass action" carbonic acid is again formed. When the cellular enzymatic changes adjust, bicarbonate reabsorption returns to normal.

Acetazolamide finds its best use in conditions in which respiratory acidosis and pulmonary disease exist. When it is effective, clinically, the effect is brought about through an increase in blood ammonia. The elevated ammonia acts as a respiratory stimulus. The increase in respiration restores the oxygen requirements of the body and reverses the

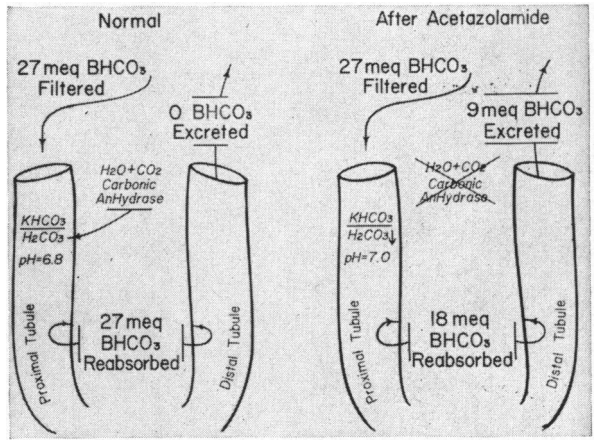

Figure 1.—Schematic representation of the effects of acetazolamide on the renal tubular reabsorption of bicarbonate.

Supported by USPHS Grant HE-07930-01 and Grant A-5356(C1) GM.

Submitted June 5, 1963.

TABLE 1.—*Dosage Schedule, Mechanism of Action and Duration of Effect of Various Sulfonamyl Diuretics*

Agent	Mechanism of Action	Dosage	Duration of Action (Hours)
Acetazolamide	Blockage of bicarbonate excretion (30 per cent) Increase of respiratory exchange	0.5 to 1 gm	6-8
Chlorothiazide	Blockage of chloride excretion (sodium, potassium and ammonia excretion simultaneously increased)	0.5 to 1 gm	6-8
Hydrochlorothiazide	" " "	50 to 100 mg	8-10
Methylchlorothiazide	" " "	2.5 to 5 mg	10-14
Benzothiodiazide	" " "	50 to 100 mg	12-14

acid-base balance to normal. In respiratory acidosis, hypochloremia is common and is the result of a shift of chloride to the intracellular compartment (primarily into red blood cells). When respiratory acidosis is corrected, the hypochloremia disappears. Occasionally, overzealous respiratory correction may cause hyperchloremia.

Acetazolamide does not improve the chemical or clinical status of a patient who is unable to increase ventilatory exchange—for example, in a patient with a fixed rib cage or a patient who is artificially ventilated. The respiratory acidosis does, in fact, become worse in these situations, due to the fact that the release of carbon dioxide across the alveolus is normally potentiated by carbonic anhydrase. If this enzyme is inhibited and ventilation is static, retention of carbonic acid ensues and respiratory acidosis becomes more severe.[8]

Acetazolamide is sometimes used to potentiate the hyperchloremia precipitated by chloride salts. However, this effect is not dramatic and the studies reporting this action were poorly controlled. Because of its inefficiency in patients without respiratory acidosis, and its weak effect even in respiratory acidosis, its clinical popularity as a drug is disappearing.

TOXICITY

Acetazolamide commonly produces ammonia intoxication, particularly in patients with hepatic disease. It does so by decreasing hepatic blood flow, thereby impeding the detoxification of ammonia entering the portal vein from the gastrointestinal tract. This effect of acetazolamide in causing ammonia intoxication is useful in stimulating ventilatory exchange in patients with respiratory acidosis, provided hepatic function is adequate. It is common to observe elevations up to 200 to 300 micrograms per 100 ml, which is sufficient to stimulate respiratory exchange beyond normal.[9]

It is rare to observe potassium depletion and metabolic alkalosis after administration of acetazolamide, since it has so slight and so transient an effect on the renal excretion of electrolytes when given in the usual therapeutic doses. If electrolyte alterations are present after the administration of acetazolamide, it is usually due to some other extraneous factor.

Respiratory alkalosis may be a complication of acetazolamide administration. However, it is usually secondary to the ammonia intoxication rather than to the drug itself.

Acetazolamide is most useful not as a clinically therapeutic agent but as a research drug. It is used in this capacity as a chemical tool to precipitate a dramatic and acute inhibition of carbonic anhydrase or to increase respiration.

THIAZIDE DIURETICS

Although strictly speaking this class of diuretics is assigned to the sulfonamyl group, their effect in man is entirely different from that of acetazolamide or other sulfonamide diuretics. Much of the confusion in the literature about these drugs has been due to the extensive experimental reports on dogs. Both groups of diuretics behave similarly in dogs and rats to block bicarbonate reabsorption. Their action is primarily on the renal excretion of sodium, chloride, potassium and water. There are four which are commonly used. All act on the same principles, although they differ in potency. The ones studied include chlorothiazide (Diuril®), hydrochlorothiazide (Hydrodiuril,® Enduron®), methylchlorothiazide and benzothiodiazide (Ureas®). The dosage schedule and potency of each agent is summarized in Table 1, which also indicates their relative effectiveness.

It is stated that the action of this oral group of diuretics is on the renal tubules, and that their action, like that of mercurial diuretics, is to block some moiety of renal reabsorption of sodium either in the distal or proximal tubules. Actually, this statement is erroneous, since they directly block

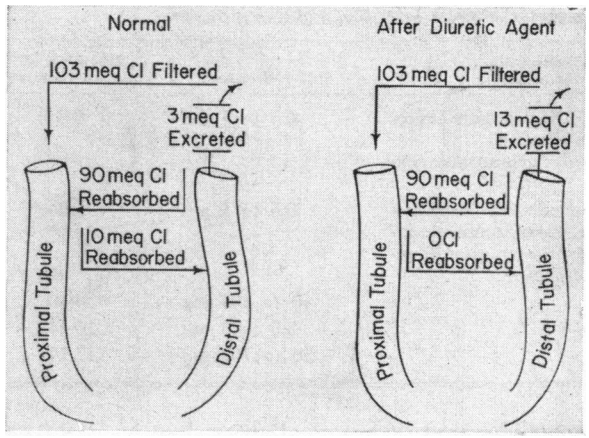

Figure 2.—Mechanism of action of thiazide diuretics.

reabsorption of chloride primarily and of sodium secondarily. If sodium reabsorption *per se* were blocked, there should be a concurrent excretion of sodium with its companion anions—bicarbonate, chloride and phosphate—in some definite relationship. However, this has not been found to be true. Chloride is the only anion which is excreted along with the cations, sodium, potassium and ammonia. These are excreted with chloride to maintain chemical equilibrium. The excretion of these ions promotes diuresis.

Theoretically, the excretion of sodium and potassium may be passive. Ammonia, of course, will depend on metabolic processes and the exchange of ammonia for sodium filtered at the glomerulus. Figure 2 outlines this hypothesis that the thiazide diuretics act, primarily, to block chloride and that cation excretion is a companion action to maintain chemical equilibrium. In support of this concept is the fact that bicarbonate, the other major anion filtered with sodium at the glomerulus, is unaffected by the thiazide diuretics.

The average dosage and duration of action of these drugs varies, but they all act in a similar manner. Although minor differences on potassium excretion may be noted, this is not a significant factor if administration of potassium salts is used to provide adequate protection. It is known that only traces of bicarbonate are excreted in the urine after thiazide administration in humans. This is in contrast to acetazolamide, which actively inhibits the renal tubular reabsorption of bicarbonate and causes an alkaline urine containing significant quantities of bicarbonate.

Refractoriness

Frequently, patients may become refractory to the oral thiazide diuretics. This is usually because of a decreased glomerular filtration rate or hypochloremia or both. If the filtration rate is decreased or if hypochloremia is present, insufficient amounts of chloride are presented to the distal tubule where it is presumed the diuretics have their blocking effect. Effectiveness can be restored by administration of chloride salts to attain hyperchloremia and set the stage for diuresis when the thiazide is subsequently administered.[8]

ACIDIFYING SALTS

It is an established fact that practically any chloride salt which is tolerated orally can be used to establish hyperchloremia* The most important consideration is that sufficient quantities must be given to be effective. Ideally, the plasma concentration should be increased to 118 to 120 mEq per liter. Calcium chloride can be given in enteric coated capsules which are mixed with a drying agent, or it can be given as a solution if tolerated in that form. Arginine hydrochloride may be used either intravenously or by mouth. Potassium chloride is also used as an auxiliary agent in a dose of 4 gm a day. Ammonium chloride cannot be used in patients with liver disease. The chloride salts are given for three to five days before the administration of the diuretic agent and are more effective if continued throughout the diuretic period. The usual dose of calcium or ammonium chloride is 8 to 10 gm a day. The usual dose of arginine hydrochloride is 25 gm a day. The acidifying salts have no diuretic effect *per se* in patients. They are only effective in potentiating the thiazide agents.†

Although the plasma pH drops (to the range of 7.1 to 7.2) when plasma hyperchloremia is established, it seldom decreases to dangerously low values. The minimum pH compatible with life is 6.8 and this value is seldom reached with the recommended dosage of chloride salt. Renal and cellular compensation are usually quite effective in preventing a severe drop in pH. Nausea and vomiting are prominent symptoms when the blood pH decreases below 7.1 and this acts as an automatic feature to prevent the pH from decreasing further. If nausea and vomiting are present, the dose of chloride salt may be too high, and it should be decreased accordingly. None of the patients so far studied has dropped below this value unless some coincident respiratory disturbances or associated acidosis existed.‡

*Theoretically, choline chloride should be effective in creating hyperchloremia. Preliminary evidence indicates that it is effective. However, there is not sufficient data available yet to offer it for clinical therapy.

†They would not be expected to potentiate the action of acetazolamide since this agent acts on the bicarbonate ion.

‡Ammonium, arginine and potassium chloride may be given intravenously if appropriate precautions are taken. Ammonium and potassium should not be given in a concentration greater than 46-60 mEq per liter of infusing media parenterally. Calcium chloride has a high degree of cardiac toxicity and should never be given intravenously.

COMPLICATIONS

The complications of the thiazide diuretics include metabolic alkalosis, sodium depletion, potassium depletion, ammonia intoxication and digitalis toxicity.

Metabolic Alkalosis

Following thiazide diuretic therapy, metabolic alkalosis may occur as the result of three factors acting collectively. They are: (1) potassium depletion favoring the renal tubular reabsorption of bicarbonate (by decreasing the intracellular pH[8,11]), (2) increased excretion of ammonium with chloride, providing for a greater renal production of bicarbonate; and (3) renal loss of extracellular fluid in excess of bicarbonate. Since the bicarbonate already present in extracellular fluid is not excreted by the kidney, its concentration in the plasma is accordingly increased, as is demonstrated in Figure 3. The increased concentration causes a metabolic alkalosis.

Metabolic alkalosis or potassium depletion or both may precipitate cardiac arrhythmia and heart failure if the patient is coincidentally treated with a digitalis glycoside. Potassium depletion and metabolic alkalosis both act to potentiate the action of digitalis in the body and toxicity may occur even though the concentration of digitalis in the body is unchanged. The mechanism whereby potassium depletion or alkalosis causes cardiac toxicity is through a change in the resting membrane potential.[11] Both cause the electromotive force (EMF) across the cell membrane to increase, thereby increasing the action potential. The neuron stimulus necessary to cause depolarization is increased and causes depolarization to become more difficult. Since cardiac glycosides also affect the membrane potential in the same direction as alkalosis and potassium depletion, these situations are additive.

This cardiac and metabolic abnormality can be corrected or prevented by the provision of at least 4 to 6 gm of potassium per day. It is usually wise to administer the potassium salt in a form to assure its absorption. Enteric coated potassium, although palatable, is not always absorbed from the intestine.

Sodium depletion infrequently occurs after thiazide diuresis and is the result of too intensive diuretic therapy without adequate sodium provision. The clinician, of course, should be cognizant of the dilutional syndrome which may cause hyponatremia. This is on the basis of retention of extracellular water: Although the total sodium in the extracellular fluid is normal, or even increased, dilution of plasma content causes hyponatremia. This condition may result indirectly from vigorous diuretic therapy, but it is usually due to excessive retention or administration of water and potassium depletion.

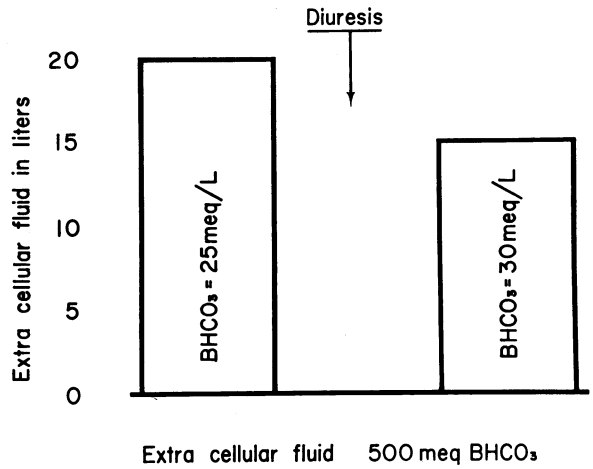

Figure 3.—Process by which use of thiazide diuretics increases concentration of bicarbonate in plasma. An assumed figure is used for the concentration of bicarbonate. As shown, if it is presumed that bicarbonate exists in a concentration of 25 mEq per liter with a total extracellular fluid of 20 liters before diuresis, the total extracellular bicarbonate is 25×20=500 mEq. If 5 liters of extracellular fluid is excreted after the diuretic is given, the total bicarbonate will be present in 15 liters instead of 20 and the concentration will be 30 mEq per liter.

Ammonia Intoxication

Ammonia intoxication is a complication peculiar to all sulfonamyl diuretics. It is due to a decrease in hepatic blood flow and subsequent impairment of the detoxification of ammonia arriving from the gastrointestinal tract. If ammonia intoxication does occur, it is easily corrected by oral antibiotics, enemas and a low-protein diet. If it is a serious complication it may be corrected with potassium or sodium glutamate. Usually, 10 to 20 gm of potassium glutamate a day is adequate. If the patient is in coma from ammonia intoxication, 80 to 100 gm of the sodium and potassium glutamate must be administered to restore consciousness.[8,9]

Hypotensive Effects

The thiazide diuretics have a weakly hypotensive effect either when given alone or in association with other hypertensive agents. The hypotensive effects are not outstanding in severe or malignant hypertension except when used in conjunction with other hypotensive agents.

Maumee Valley Hospital, 2025 Arlington Ave., Toledo, Ohio 43609.

REFERENCES

1. Aleksandro, D., Wysznacka, W., and Gajewski, J.: Influence of Chlorothiazide upon arterial responsiveness to nor-epinephrine in hypertensive subjects, New England J. Med. 261:1052, November 9, 1959.

2. Ford, R. V.: Comparative effects of benzydroflumethiazide and hydrochlorothiazide on urinary electrolyte excretion, Current Therap. Res., 2:92, March, 1960.

3. Ford, R. V.: The clinical pharmacologic investigation of a new benzothiadiazine diuretic, Current Therap. Res., 5: 407, March, 1960.

4. Ford, R. V., Moyer, J. H. and Spurr, C. L.: Clinical and laboratory observations on chlorothiazide (Diuril®), Arch. Int. Med. 100:582, 1957.

5. Hwang, K., Iwamoto, H. K., Coen, L. and Johnson, H. E.: Diuretic effect of some 2- and 3- substituted analogues of hydrochlorothiazide, Fed. Proc., 19:363, 1960.

6. Nickell, J. and Ford, R.V.: Clinical pharmacologic observations on Oretic, a new orally active diuretic agent, Current Therap. Res., 1:25, 1959.

7. Pitts, D. F.: Mechanism of Action and Therapeutic Use of Diuretic Agents, Charles C. Thomas, publisher, 1959.

8. Roberts, K. E.: Clinical Physiology, Filmer Bros. Press, San Francisco, 1960.

9. Roberts, K. E.: Ammonia intoxication, S. Car. Med. J., 33:1, 1957.

10. Roberts, K. E., Magida, M. G.: Electrocardiograph alterations produced by a decrease in plasma pH, bicarbonate and sodium as compared with those produced by an increase in plasma potassium, Circ. Res., 1:206, 1953.

11. Roberts, K. E., Randall, H. T., Vanamy, P. and Poppell, J. W.: Bicarbonate metabolism, Metabolism, 4:404, 1956.

12. Symposium on chlorothiazide and other diuretic agents, Am. N. Y. Acad. Sc., 71:32, 1958.